REMARKS

Applicant respectfully requests entry of amendments to claims 7, 17, 18-20, 21, 22, 24, 25, and 26-28, and to please cancel claim 8. Please withdraw claims 1-6 and 9-15, without prejudice or disclaimer.

Support for the amendments can be found throughout the specification, including Tables I and II; page 7, lines 5-20; page 8, line 23 to page 9, line 10; page 11, line 1; Figure 1, including the legend to figure 1; page 16, lines 27-29; page 20, lines 2-3; page 36, lines 2-7; sequence identifiers (SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, and the sequence listing), and the originally filed claims, and, therefore, do not add new matter.

Applicant submits that pending claims 7 and 16-28 are in condition for allowance, and respectfully requests that the claims as amended be entered.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 7 and 16-28 stand rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite.

Applicant traverses the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

Claim 7 no longer recites "in reading frame," so the rejection is rendered moot. Applicant has amended the claim to recite "wherein the carboxy-terminal residue of the first polypeptide is operably linked to the amino-terminal residue of the second polypeptide." The present construction would be known to one of skill in the art generally as linkage of two polypeptides, including their orientation relative to one another. As such, one of skill in the art would understand the metes and bounds of the term.

Regarding "multimeric polypeptide of trimer units," Applicant would point out that this recitation is directly supported by Figure 1, including the legend to Figure 1, where the Figure clearly shows that a tetramer (i.e., multimeric CD40L-SPD) comprises 4 timer units. Each trimer unit comprises three trimer strands (see "MONOMER" Figure 1), and each trimer strand is a fusion protein comprising a first portion from a collectin family scaffold protein (i.e., comprising the hub and body region of the protein) and a second portion from a TNFSF ligand (i.e.,

comprising the extracellular domain of the ligand). Accordingly, a "multimeric polypeptide of trimer units" would be multiples of monomers which bind at the hub. In the legend to Figure 1 such a conformation is described as a "tetramer," which is at least a dimer of trimer units. Therefore, because the specification clearly delimits the phrase at issue, one of skill in the art would understand the metes and bounds of the claims.

Regarding "wherein the amino acids comprising a carbohydrate recognition domain (CRD)," while not acquiescing to the reasoning offered in the Action, and to expedite prosecution toward allowance, the claim has been amended to provide antecedent support.

Regarding "100 to 250 amino acids comprising an extracellular domain," while not acquiescing to the reasoning offered in the Action, and to expedite prosecution toward allowance, the claim has been amended to provide antecedent support.

Regarding claims 18 and 19, referring to "trimer unit is a homotrimer" and "trimer unit is a heterotrimer," respectively, while not acquiescing to the reasoning offered in the Action, and to expedite prosecution toward allowance, the claims have been amended to more clearly define the invention.

Regarding claim 20, while not acquiescing to the reasoning offered in the Action, and to expedite prosecution toward allowance, the claim has been amended to more clearly define the invention.

Regarding claim 27, while not acquiescing to the reasoning offered in the Action, and to expedite prosecution toward allowance, the claim has been amended to provide antecedent support.

Regarding claim 28, while Applicant does not acquiesce to the reasoning offered in the Office Action, and to expedite prosecution toward allowance, the claim has been amended such that the multimer of the claim is a dimer.

For these reasons, Applicant respectfully requests that the rejection be withdrawn.

Rejection Under 35 U.S.C. §112, First Paragraph

Claim 7 stands rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking written description support.

Applicants traverse the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

The Office Action alleges, in pertinent part, that the specification does not disclose "in-reading frame" in the disclosure as originally filed. Further, the Action intimates that the N- and C-terminus residues of the first and second polypeptides, as well as replacement of the CRD by the extracellular domain do not find support in the specification as filed. Applicant respectfully submits that such allegations are incorrect.

Regarding "in-reading frame" notwithstanding the arguments below, this element is no longer recited in the claims, therefore, the rejection as it relates to this element is rendered moot.

Applicant submits that the specification expressly states:

> "The C-terminus of each collectin contains a CRD which binds carbohydrates and other ligands. Because of the tight similarities between the known CRD structures and the extracellular domains of TNFSF members, it is likely that the CRD of any collectin could be replaced with the extracellular domain of any TNFSF member in a structurally compatible manner." (Page 36, lines 2-7).

Further, the specification also states that:

> "An analysis of the CRD crystal structure of another collectin, ACRP30, indicated that it was structurally superimposable upon the crystal structures of the extracellular regions of CD40L, TNF, and Fas [Shapiro, 1998]. The successful expression of the collectin TNFSF fusion protein, CD40L-SPD, indicates that other TNFSF members (Table I) could be cojoined to SPD in a similar manner and that other collectins besides SPD (Table II) could be used as a protein framework instead of SPD." (Page 28, lines 19-24).

A protein search of the three TNFSF ligands cited above shows that each has an extracellular domain (ECD) in the C-terminal region of the protein, wherein each of these domains comprises between about the last 100 to 138 amino acids of the C terminus of these

ligands (see, e.g., GenBank Accession Nos. NP_000065 [CD40L]; NP_000585 [TNF]; and NP_032013 [Fas]). The specification also states that the second sequence, expressing a portion of the TNFSF stalk, can be from base 800 to base 1528 of SEQ ID NO:5 (see page 8, lines 12 and 13). Such a region would encode about the last 250 amino acids of CD40L (a TNFSF ligand).

A search of the CRD domains for the collectin superfamily members as listed in Table 2 demonstrates that these domains occupy the C-terminal region of these proteins, wherein each domain comprises between about the last 100-250 amino acids of the C-terminus of these domains (see, e.g., GenBank Accession Nos. NP_031598 [C1q]; NP_000233 [mannose binding protein, MBL1]; and AAB35626 [ACRP30]). Applicant submits that the regions of the collagenous domains for these sequences (i.e., the regions comprising the hub and body portions which assist in trimer formation) are contained in the N-terminal region for each of the listed collectins. Further, the length of the corresponding region expressed from the nucleic acids as exemplified by the sequence identifiers recited on page 8, lines 10-13, would represent the first about 250 amino acids of SP-D (a collectin family scaffold protein).

Moreover, to paraphrase the Amendment of December 20, 2005, the claims as presently recited describe 1) the orientation of the sequences making up the fusion polypeptide, 2) the order of the requisite domains in the fusion polypeptide, and 3) the minimal and maximal lengths of the included component domains for the fusion polypeptide (i.e., the hub and body region of the collectin polypeptide, minus the CRD, and the ECD TNFSF polypeptide, minus the intracellular and transmembrane domains), where the structure/function of the domains and polypeptides disclosed in the invention are *defined and well known in the art*.

Again, when the achieved novelty resides in the *combination* of the segments of known genes, the specification is not limited to being the only source of knowledge to meet the standard for written description regarding these elements (see, e.g., Capon v. Eshhar, 76 U.S.P.Q.2d 1078 (Fed. Cir. 2005)). Further, there is no *per se*, *ipsis verbis* requirement to meet the written description standard (see, e.g., Fujikawa v. Wattanasin, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996)), all that is required is that the disclosure reasonably convey to the skilled artisan possession of the subject matter at issue (Id.). And, in view of the holdings in Capon, the requirement that the

elements as recited must be analyzed and reported afresh in the specification, where the structure and function of the recited elements are known, is not the standard for written description (Id.).

Therefore, given 1) the crystal superimposability of the collectin CRDs and TNFSF ECDs; 2) the defined and art recognized domain structure and function for the CRDs and ECDs, including the known boundaries of each domain for each member comprising the protein family; and 3) the recited lengths of the domains comprising the sequence identifiers as recited in the specification for functional trimer strands/trimer units, the delimiting lengths/domains as recited which define the fusion protein as claimed do not represent new matter, even if not every nuance of the claim is explicitly described in the specification (see, e.g., In re Alton, 37 U.S.P.Q.2d 1578 (Fed. Cir. 1997)).

As such, one of skill in the art could envision the structural/functional details of the fusion trimer strand of the claimed invention, including the domain structure of the component polypeptides, and would appreciate that the Applicant was in possession of the invention as claimed at the time the present application was filed.

For these reasons, Applicant respectfully requests that the rejection be withdrawn.

Rejection Under 35 U.S.C. §103

Claims 7 and 16-28 stand rejected under 35 U.S.C. §103 as allegedly being unpatentable over Hoppe et al. in view of Maraskovsky et al.

Applicant traverses the rejection as it might apply to the amended claims, including claims dependent therefrom, for the reasons given below.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First there must be some suggestion or motivation in the references themselves or in knowledge generally available to one of skill in the art, to modify the reference or combine the reference teachings. Second, there must be a reasonable expectation of success. And, finally the prior art reference (or references when combined) must teach all claim limitations. The teaching or suggestion and reasonable expectation of success must both be found in the prior art and not in Applicant's disclosure. (See M.P.E.P. §706.02(j)).

Applicant submits that because the cited references teach away from the present invention, and in fact, as the present invention would represent an unexpected result in view of the teachings of the cited references, one of skill in the art would not be motivated to combine the cited references.

The Office Action alleges, in pertinent part, that Hoppe et al. is silent with respect to teaching the fusion of collectin polypeptide to TNFSF polypeptide. The Action then provides Maraskovsky et al. to cure the deficiency identified in the primary reference. However, review of Hoppe et al. demonstrates that the reference does not teach a soluble trimerizing polypeptide, an element presently recited in the claims.

Hoppe et al. provides the following cautionary note:

> "Although the present invention is generally applicable, not all protein domains may be used with the neck region equally well. Very large domains may require specially adapted linker sequences and, most importantly, domains which show dimerizing or oligomerizing properties can form large aggregates which could be entirely insoluble or otherwise unsuitable for the use they were intended for." Col. 5, ll. 36-42.

It is well known in the art that TNFSF members have the common feature of forming trimeric structures; i.e., they possess "domains which show dimerizing or oligomerizing properties" (see, e.g., Exhibit A). Thus, based on the express teachings of Hoppe et al., such domains would be expected to "form large aggregates which could be either entirely insoluble or otherwise unsuitable for the use they were intended for."

Single chain antibodies are chimeras of the variable regions of the heavy and light chains of immunoglobulin, linked together with a short linker, usually serine or glycine (see, e.g., Exhibit B). As the single chain antibody possesses epitope binding properties, this demonstrates that the heavy and light chains oligomerize (i.e., intra-strand) to form an antigen binding domain. Thus, single chain antibodies would possess the domains that are specifically "taught away" by the reference, i.e., those domains which would result in insoluble products.

Further review of Hoppe et al. demonstrates that an attempt was made to construct a fusion protein comprising a single chain antibody; i.e., a fusion protein which contains "domains which show dimerizing or oligomerizing properties" (see Example 6).

Hoppe et al. expressly states:

> "Expression levels were found to be similar to that obtained with the neck-region alone (Example 1) (see FIG. **18**). However, following the purification protocol, as outlined in example 1, most of the fusion protein was found to be insoluble and only a small proportion of the single-chain antibody fusion proteins could be solubilized and purified using a glutathione-agarose affinity column." Col. 20, ll. 3-9. (Emphasis added).

As can be seen from the quote above, the prediction as proffered was indeed correct; i.e., fusion proteins containing domains which show dimerizing or oligomerizing properties were insoluble. Applicant submits that in view of this evidence alone the cited reference "teaches away" from the present invention. One of skill in the art would only extract from such a teaching that fusion proteins as claimed would produce insoluble products (i.e., fusion protein comprising domains which show dimerizing or oligomerizing properties). As such, the reference does not teach the purpose of obtaining a soluble multimer as claimed, and thus, the purpose of Applicant's invention could not be accomplished using the teachings of the cited reference. Therefore, the reference teaches away, since the impression left to the skilled artisan is that the product would not have the property sought by Applicant. In re Caldwell, 319 F.2d 254, 256, 138 U.S.P.Q. 243, 245 (CCPA 1963).

Nevertheless, Applicant also submits that the solubilized single chain antibody containing product in Hoppe et al. does not contain a collagen triple helical structure, as demonstrated below.

Further review of Hoppe et al. shows that the reference expressly teaches a method for determining the presence of a collagen triple-helical structure. At col. 18, ll. 23-41 (Example 4), the reference expressly recites the following:

> "Upon digestion with thrombin and subsequent SDS-PAGE analysis marked differences were seen in the sizes of the cleavage products. The fusion protein

consisting of the glutathione-S-transferase and the 48 Gly-Xaa-Yaa triplets only gave rise to a large number of peptides of different length, reflecting the frequently occurring cleavage by thrombin of peptide bonds involving arginine residues within the collagenous sequence (data not shown). In contrast, the glutathione-S-transferase fusion protein containing the neck-region peptide C-terminal to the 57 Gly-Xaa-Yaa triplets and the N-terminal non-collagenous peptide from human SP-D showed only a single cleavage into two products, the glutathione-S-transferase and the entire collagenous region with the neck-region peptide and the N-terminal peptide of human SP-D attached (FIG. 14). As the 48 Gly-Xaa-Yaa triplets of the first construct were contained in the 57 Gly-Xaa-Yaa triplets of the second construct, the absence of thrombin cleavage at any of the arginine residues is consistent with the presence of collagen triple-helical structure." (Emphasis added).

Thus, Applicant submits that based on this observation (as exemplified by the underlined statement), the presence of additional cleavage products after digestion with thrombin would be inconsistent with the presence of collagen triple-helical structure.

Example 6 of Hoppe et al. further recites the following:

> "Upon cleavage with thrombin fragments of the expected size were detected using SDS-PAGE analysis. Minor amounts of smaller fragments were also seen." Col. 20, ll. 11-12. (Emphasis added).

Applicant submits that, as evidenced by the inventor's own procedure, the solubilized product has a configuration that is inconsistent with a collagen triple helical structure, as exemplified by the presence of additional cleavage products after digestion with thrombin; i.e., cleavage products would not be expected if a collagen triple-helical structure were present.

Further, while it can be argued that Hoppe et al. suggest that a means to "obtain improvement of yield and structural uniformity of the expressed antibody constructs may be obtained by following standard protocols for purification of recombinant proteins from bacterial inclusion bodies [20] or the use of a yeast expression system, known to facilitate expression of disulphide containing molecules," (col. 20, ll. 29-33, emphasis added) these were neither

accomplished nor attempted in the cited reference. More importantly, Applicant did not require the use of any of these suggested steps to achieve the fusion protein as claimed.

Applicant would submit that the inability to achieve a soluble fusion protein using the teachings of Hoppe et al. is not merely a theoretical proposition (solubility and structural uniformity for intended use [e.g., formation of soluble multimers at the trimerized hub] being *requisite properties* of the fusion trimer strand of the instant invention), but that in fact achieving the multimer as claimed is an impossibility in view of the teachings of Hoppe et al. At minimum, based on the teachings of Hoppe et al., obtaining an *entirely* soluble trimerizing fusion protein containing oligomerizing (i.e., TNFSF) domains would be an unexpected result. And while the suggestion offered in Hoppe may provide an "obvious-to-try" rationale, obvious to try is not the standard under § 103. In re O'Farrell, 853 F.2d 894, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988). Thus, Applicant submits that there can be no reasonable expectation of success based on the reference teachings.

Accordingly, as there is no reasonable expectation of successfully achieving a *entirely* soluble fusion protein comprising domains which show dimerizing or oligomerizing properties having a collagen triple-helical structure using the teachings of Hoppe et al., whether Maraskovsky et al. teach or does not teach that CD40L polypeptides may be created by fusion of the C-terminal of soluble CD40L to the Fc region of IgG1 is immaterial.

Again, the "teaching or suggestion **and** reasonable expectation of success must **both** be found in the prior art." (Emphasis added). One cannot simple use the Applicant's disclosure as a "blueprint" to reconstruct, by hindsight, Applicant's claim. See, e.g., Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985). Because there is neither the suggestion nor reasonable expectation of success that can be found in the cited art, no *prima facie* case of obviousness has been established.

Because the teachings of Hoppe et al. would not result in soluble multimer as claimed when combined with the teachings of Maraskovsky et al., one of skill in the art would not have an expectation of success since the invention as claimed would not be achieved in view of such teachings. Therefore, one of skill in the art would not be motivated to combine such teachings.

Applicant submits that because there is no reasonable expectation of successfully achieving the invention as claimed, there is no motivation to combine the cited references, thus, no *prima facie* case for obviousness exists. For these reasons, Applicant respectfully requests that the rejection, including as it might be applied against the amended claims, be withdrawn.

Conclusion

In view of the above amendments and remarks, Applicant submits that pending claims 7 and 16-28 are in condition for allowance. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this submission.

No fee is deemed necessary with the filing of this paper. However, the Commissioner is hereby authorized to charge any fees required by this submission, or credit any overpayment, to Deposit Account No. 07-1896 referencing the above-identified docket number. A copy of the Transmittal Sheet is enclosed.

Respectfully submitted,

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